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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,677	10/01/2001	Samuel J. Davis	REG 670A-US	3022

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EXAMINER	
O HARA, EILEEN B	
ART UNIT	PAPER NUMBER
1646	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/868,677	Applicant(s) DAVIS ET AL.	
	Examiner Eileen O'Hara	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-88* is/are pending in the application.

4a) Of the above claim(s) *53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-52 and 55-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *42-88* ~~are~~ subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 42-88 are pending in the instant application.

Election/Restrictions

2. Applicant's election of the species of ligand binding domain of angiopoietin in Paper No. 9 is acknowledged.

Claims 53 and 54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No.9.

Claims 42-52 and 55-88 are currently under examination.

Specification

3. The disclosure is objected to because of the following informalities:

Applicants are advised that the official first page of the specification is the substitute sheet that was entered during prosecution of the PCT application, which had a different priority statement from that of the original first page. In preliminary amendment A, filed October 1, 2001, the amendment to insert the priority information on line 3 resulted in a duplication of some of the priority information, and the retention of the original information, which had an incorrect date. It is recommended that Applicants amend the specification to replace the priority information.

Appropriate correction is required.

Claim Objections

4. Claims 44, 47 and 48 are objected to because of the following informalities:

4.1 In claim 44, the word "then" on the third line should be replaced with the word "than" to be grammatically correct.

4.2 In claims 47 and 48, the word "if" on the second line of the claims should be replaced with the word "of" to be grammatically correct.

4.3 Claims 51 and 52 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 42 and each other. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 58 and 76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. Claims 58 and 76 encompass fusion polypeptides wherein the immunoglobulin derived domain can be the constant region domain of IgG, and the specification and claims as originally filed did not disclose that the constant region domain of IgG could be the immunoglobulin derived domain (see page 9, lines 18-25, for example).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 42-48, 51, 52 and 55-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42-48, 51, 52 and 55-70 are vague and indefinite because claims 42, 51 and 52 encompass a nucleic acid molecule encoding a fusion polypeptide, wherein the first subunit comprises at least one copy of ***a*** receptor binding domain of a ligand, and the second subunit comprises at least one copy of ***the*** receptor binding domain of a ligand. As written, there can only be one receptor binding domain for the second subunit ligand, but there may be more than one receptor binding domain for the first subunit ligand, so it is not clear exactly what is being claimed, especially in view of the fact that some dependent claims (for example claim 43) that limit the two receptor binding domains in the fusion protein as being derived from the same ligand. The other claims are rejected for depending from claim 42.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 42-44, 51, 52, 59-61, 63-67 and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Pack et al., WO 96/37621, Nov. 28, 1996 (cited by Applicants).

Claims 42-44, 51, 52, 59-61, 63-67 and 70 encompass nucleic acid molecules encoding a fusion polypeptide wherein the fusion polypeptide comprises a first subunit comprising at least one copy of a receptor binding domain of a ligand, the first subunit being fused to the N-terminal end of a multimerizing component, and the multimerizing component being fused at its C-terminal end to a second subunit comprising at least one copy of the receptor binding domain of a ligand, wherein the first and second subunits may be derived from the same or different ligands, the encoded fusion protein, wherein the fusion polypeptide is multimerized, composition comprising the multimerized fusion polypeptide, expression vector in which the encoding nucleic acid is operably linked to an expression control sequence, host-vector system for the production of the fusion polypeptide wherein the host may be E. coli, a yeast or mammalian cell, and method of recombinantly producing the fusion polypeptide.

Pack et al. teach DNA sequences encoding multimeric fusion proteins (see entire patent and page 9, second paragraph) comprising two or more functional domains which may have the structure described on pages 16-17 which has a first functional domain fused to a multimerization device (amino acids), which in turn is fused to a second functional domain (with

linkers) which is structurally the same as the nucleic acid of claim 42 (claims 1 and 19 of Pack et al.), encoded protein (pages 19-20 and claims 29-33), in which the functional domain may be a polypeptide which can bind a receptor binding site (ligand), (see last paragraph of page 16), wherein the first and second subunits may be derived from the same or different ligands (page 13, lines 1-20, and paragraph bridging pages 13 and 14, page 23, second paragraph, page 8, last paragraph to page 10, line 11 and claims 32 and 33). Pack et al. also teach multimerized fusion polypeptide (claims 31-33) compositions comprising the fusion polypeptide (claim 39), expression vector in which the encoding nucleic acid is operably linked to a regulatable promoter (expression control sequence), host-vector systems wherein the host may be E. coli, a yeast or mammalian cell, and method of recombinantly producing the fusion polypeptide (page 24, line 17 to page 25, line 12, paragraph bridging page 19 and 20, claims 34-37). Thus, the claimed invention is anticipated by Pack et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 45-50, 55-58, 62, 68-69 and 71-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pack et al., WO 96/37621, Nov. 28, 1996, and further in view of Davis et al., US Patent No. 6,265,564, filing date Oct. 25, 1996, and further in view of Desnick et al., US Patent No. 5,580,757, Dec. 3, 1996.

Claims 45-50, 55-58, 62, 68-69 and 71-88 encompass nucleic acids encoding fusion proteins wherein the receptor binding domain may be anigopoietin-1 or anigopoietin-2, or nucleic acids encoding fusion proteins that comprise more than one copy of a receptor binding domain of a ligand, each copy fused in tandem, and wherein either the N-terminal or the C-terminal ends of the tandem receptor binding domains is fused to a multimerizing component, suitable host cell that is a COS or CHO cell, that the fusion protein can be a dimer, or that the multimerizing component may be an immunoglobulin derived doman that may be Fc.

The teachings of Pack et al. are summarized as above. Pack et al. does not teach the limitations of the above claims. Pack et al. teach on page 1, second paragraph, that multivalency is a prerequisite for a variety of macromolecular interactions such as ligand recognition and activation or inhibition of receptors, and on page 2, middle paragraph, that the enhancement of weak monovalent forces by multiplying the number of interactions is increasingly used for protein engineering and therapeutic applications.

Davis et al. disclose TIE-1 and TIE-2 ligands, which are the same proteins as angiopoietin-1 and angiopoietin-2, respectively, and teach that the two ligands both bind the

TIE-2 receptor. TIE-1 ligand is an agonist of the TIE-2 receptor, and TIE-2 ligand is an antagonist of the TIE-2 receptor. Both ligands contain a "coiled coil" domain and a fibrinogen-like domain. Davis et al. constructed fusion proteins comprising domains of the TIE ligands and Fc domain of IgG, and teach that the Fc section of human antibody IgG1 dimerizes upon expression by mammalian cells (column 44, lines 17-34). Davis et al. disclose experiments in which they demonstrate that the "coiled coil" domain functions as a multimerizing component and the fibrinogen-like domain is the receptor binding domain, but that monomeric forms of the fibrinogen-like domain do not bind the receptor unless they are joined to a "coiled coil" domain, an Fc domain, or myc-tag and "clustered" using anti-myc antibodies. Davis et al. also teach that the TIE ligands can only bind in dimeric, trimeric or higher multimeric forms, and that the dimeric form of the fibrinogen-like domain of either TIE-1 or TIE-2 fused to Fc can bind the TIE-2 receptor, whereas monomeric forms cannot (column 18, line 39 to column 19, line 11, column 43, line 40 to column 44, line 60, and Table 1).

Desnick et al. teach eukaryotic host-expression systems using COS or CHO cells, and advantages of using these cells. At column 14, lines 14-27, Desnick states:

> "Although prokaryotic systems offer the distinct advantage of ease of manipulation and low cost of scale-up, their major drawback in the expression of .alpha.-Gal A is their lack of proper post-translational modifications of expressed mammalian proteins. Eukaryotic systems, and preferably mammalian expression systems, allow for proper modification to occur. Eukaryotic cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, phosphorylation, and, advantageously secretion of the gene product should be used as host cells for the expression of .alpha.-Gal A. Mammalian cell lines are preferred. Such host cell lines may include but are not limited to CHO, VERO, BHK, HeLa, COS, MDCK, -293, WI38, etc."

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to make fusion proteins comprising one or more domains of

receptor binding domains of a ligand or ligands such as angiopoietin-1 and/or angiopoietin-2, either separated by a multimerizing component such as Fc domain of IgG or in tandem, since Pack et al. teach that many receptors can't be activated unless the ligands bind in multimeric form and fusion proteins can be constructed providing these multimeric and more active forms which can be used therapeutically. Alternatively, multimeric fusion proteins can be used in a research setting, in order to determine, for example, if fusion proteins comprising domains from different ligands have new and useful properties. Since Davis et al. teach that the Fc domain of IgG can multimerize proteins fused to it and that both angiopoietin-1 and angiopoietin-2 can't bind the TIE-2 receptor as monomers, it would also have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use Fc domain of IgG as the multimerizing component, and to make such constructs using the receptor binding domain of angiopoietin-1 and/or angiopoietin-2. It would also have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to produce the fusion proteins in COS or CHO cells, since Desnick et al. teach the advantages of using these cells to produce biologically active eukaryotic proteins. The skilled artisan would be motivated to make these fusion constructs since these constructs would be useful either therapeutically or for research purposes, as discussed above, and given that the state of the art of molecular biology is high, such fusions can easily be constructed and expressed in cells. There would be a reasonable expectation of success, since the methods of making such fusion proteins are well-established and have resulted in similar proteins with desirable properties.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Eileen B. O'Hara

Patent Examiner